

Prevalence of allergic sensitization versus allergic rhinitis symptoms in an unselected population

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Abstract

Background: Allergic rhinitis (AR) is the most common allergic disorder and its prevalence has significantly increased worldwide, nowadays affecting up to 40% of the population in young adults. The objective of the present survey was to evaluate the prevalence of allergic sensitization and the prevalence of clinically diagnosed AR in a sample of the Belgian population, and to estimate the effect of age and gender.

Methods: We performed a cross-sectional population-based study on an annual public fair in Ghent. Participants underwent a skin prick test (SPT) to 3 aeroallergens: mix of trees (hasel, alder, birch), grass pollen and house dust mite (HDM). The clinical relevance of sensitization was assessed by relating relevant symptoms of AR to the corresponding SPT.

Results: 2320 participants (1475 females, median age of 44.7 years, range 3y-86y) were included in this study. Standardized prevalence rates of sensitization were 13.2% for tree mix, 25.9% for grass pollen and 25.9% for HDM. Sensitization to at least one of the allergens was present in 40.3% of the subjects. Symptomatic sensitization related to trees was reported in 9.7%, grass related AR was 17.6% and HDM related AR 17.1%. The overall prevalence of AR was 30.9%.

Conclusion: In this study we demonstrated a 40.3% prevalence of a positive SPT to one or more common aeroallergens. A clinical diagnosis of AR was present in 30.9%, peaking in the third and fourth decade of life. It is to be expected that in the next decades, when this generation will grow older, the general AR prevalence will further increase.

Introduction

Allergic rhinitis (AR) is the most prevalent form of non-infectious rhinitis, inflammation of the mucous lining of the nose. Symptoms of AR include rhinorrhea, congestion, nasal itching and sneezing. This type of rhinitis is caused by an IgE-mediated reaction to environmental allergens such as house dust mite (HDM), and pollen from grass and trees (1).

Allergic rhinitis poses a considerable burden on public health because of its prevalence, impact on quality of life, productivity, economic costs and asthma comorbidity (1-3). It represents a growing global health problem, nowadays affecting up to 40% of the population (2). Despite the widely recognized burden of allergy, there is insufficient data on the epidemiology of allergic rhinitis (1). A wide variety between countries in prevalence of sensitization can be observed (2). Most population-based epidemiologic studies define allergic rhinitis based on questionnaires with varying diagnostic criteria (4-6). There is a clear lack of epidemiological studies, reporting a clinical diagnosis of allergic rhinitis in the general population.

Skin prick testing (SPT) is the standard of care in diagnosing IgE mediated allergy. However, not all rhinitis patients have a positive SPT, and not all patients with a positive SPT perceive allergic symptoms (7). Few studies report SPT prevalence in an unselected population-based sample.

The objective of the present survey was to evaluate the prevalence of allergic sensitization and the prevalence of clinically diagnosed AR in a population-based sample of the Belgian population at an annual public fair, and to evaluate the effect of age and gender on sensitization and presence of symptoms in sensitized subjects.

Methods

Study design

The study was designed as a cross-sectional population-based study. Subjects were sampled from visitors of an annual public fair in September 2008 in the city of Ghent, Belgium. Here, we organized a stand about allergic disease, and visitors were invited to undergo a SPT by means of visual information about allergic disease. Subjects were required to understand the procedure and gave oral consent. The study is approved by the local ethical comite.

SPT was performed by otolaryngologists, dermatologists and allergy nurses. The used allergen panel consisted of a tree mix (hasel, alder, birch), grass pollen mix (*Phleum*, *Dactylis*) and *Dermatophagoides pteronyssinus*, each at a concentration of 100 I.R./mL (ALK Abello, Horsholm, Denmark). Histamine and saline were used as positive and negative control. Each subject was tested on the forearm using stainless steel lancets (ALK Abello, Horsholm, Denmark). After 15 minutes, the size of each wheal was documented as the mean of the longest diameter and the longest diameter perpendicular to it. A positive reaction was defined as a mean wheal size of at least 3 mm, after subtraction of the negative control.

Subjects having a positive SPT were questioned about symptoms (watery anterior rhinorrhoea, sneezing, nasal obstruction) and in which months these occur. Next, the examiner evaluated whether the subjects' symptoms were related to the sensitizations found in the SPT. For each allergen, symptoms were coded by the examiner as 'no relevant symptoms', 'current relevant symptoms', 'past relevant symptoms', or 'unknown symptoms'. Allergy was considered symptomatic when at least one of the symptoms was present, corresponding allergen exposure with its seasonal pattern (perennial for HDM, seasonal for grass or tree pollen; specific pollen seasons were provided by local pollen monitoring agencies). No strict diagnostic criteria were applied, and diagnosis based on clinical history and SPT was made by the examiner.

68

69 *Statistical analysis*

70 As over 80% of the public fair visitors were originating from the region of Flanders, Belgium,
71 prevalences were weighted for age and sex to the Flemish reference population (8) using
72 direct standardization. Standardized prevalences were estimated using intervals based on Fay
73 and Feuer (9). Logistic regression, weighted for age and sex, was used to estimate risks of age
74 and sex for each outcome. All reported odds estimates were mutually adjusted. P-values less
75 than 0.05 were seen to indicate statistical significance. Missing data were considered to be
76 missing completely at random. All statistical analyses were carried out using STATA v.11.1
77 (StataCorp, College Station, TX, USA) with the DISTRATE module for direct
78 standardization (10).

Results

Population characteristics

In total, 2320 participants, who all underwent SPT, were included in this study. The group consisted of 1475 females (63.6%) and had a median age of 44.7 years (range 3-86 y, IQR 26–62 y). Compared to the Flemish reference population, there were slightly more women and older aged subjects.

Prevalence of sensitization

Table 1 shows unstandardized and age and sex standardized prevalence rates of sensitization. Standardized prevalence rates of sensitization were 13.2% for tree mix, 25.9% for grass pollen, and 25.9% for HDM. Sensitization to at least one of the allergens was present in 40.3%.

We estimated the effect of age and sex on sensitization (Table 2 and Figure 1). Compared to women, men had an increased rate of sensitization to HDM ($p=0.001$) and a tendency towards an increased rate of grass sensitization ($p=0.074$), but not for trees ($p=0.115$). For all allergens, there was an increase in sensitization in the third and fourth age decades, compared to first two decades. In women, sensitization prevalence peaked between the age of 20 and 29 at 58.3% (95% CI: 51.9%-64.8%), while in men, the highest prevalence of 60.9% (95% CI: 50.7-71%) was found in those aged 30-39 years old. After this peak, the prevalence decreased with increasing age in both sexes (test for trend $p<0.001$).

Prevalence of symptomatic sensitization

The majority of subjects provided information on allergy related symptoms. Of all subjects, 57 did not provide answers to the questions about sensitization to trees, 75 to grass pollen, and 80 to HDM. Because few people answered 'past relevant symptoms' (tree mix: 0, grass pollen:

5, HDM: 6) and 'unknown symptoms' (tree mix: 16, grass pollen: 42, HDM: 47), these answers were excluded from analysis.

Symptomatic sensitization (AR) related to trees was reported in 9.7% (Table 1). Grass-related AR was reported in 17.6% and HDM-related AR in 17.1%. The overall prevalence of AR (sensitization and relevant symptoms) was 30.9%. There were no significant sex differences in prevalences of allergen-specific symptomatic sensitizations, but overall prevalence of AR was more prevalent in men compared to women ($p=0.023$). The age pattern of AR closely resembled the pattern of sensitization (Table 2 and Figure 1).

Symptom presence in sensitized subjects

In those with a positive SPT to tree mix, 81.1% (95% CI: 75.0%-87.3%) experienced nasal symptoms, while 73.1% (67.5-78.7%) of grass-sensitized and 72.8% (68.5-77.2%) of HDM-sensitized subjects experienced nasal symptoms. Overall, 81.0% (77.8-84.1%) of sensitized subjects had nasal symptoms.

In sensitized subjects, we estimated the effect of age, sex, and wheal size on symptom presence using logistic regression (Table 3). Men were less likely to report symptoms in those sensitized to grass (OR 0.51; $p=0.042$) and to HDM (OR 0.58; $p=0.035$) but not in those sensitized to trees (OR 0.81; $p=0.642$). There was no effect of age on symptom presence. An increased wheal size was associated with the presence of symptoms in grass sensitized (OR 1.16 per mm increase; $p=0.008$) and HDM sensitized (OR 1.26; $p<0.001$) subjects, but not in tree sensitized subjects (OR 1.82; $p=0.115$). In those sensitized to any allergen, we tested the effect of age, sex and number of sensitizations on the presence of symptoms. There was no association of symptom presence with age (p for trend=0.63) or sex ($p=0.108$). The number of sensitizations strongly increased the presence of symptoms (OR 2.26, $p=0.001$ for 2 vs 1 sensitization; OR 3.06, $p=0.01$ for 3 vs. 1 sensitization; test for trend $p<0.001$).

129

130 *Sensitization patterns*

131 Sensitization prevalences to only one allergen group were 2.8% (95% CI: 2.1-3.5%) for tree
132 mix, 7.8% (6.5-9.0%) for grass pollen and 10.7% (9.3-12.1%) for HDM.

133 We compared the observed prevalence of sensitization to different allergen groups to the
134 prevalence that was expected if a combination would occur by chance alone (Table 4).

135 Expected prevalences were calculated as the product of the prevalences of sensitizations to
136 one single allergen group. All combinations had a prevalence that was significantly higher
137 than expected. Among combinations of two allergen groups, the combination grass pollen and
138 tree mix showed the highest observed/expected ratio of 18.3, and the ratio of sensitization to
139 all three allergen groups was 229.5 times the expected prevalence.

Discussion

We evaluated the prevalence of allergic sensitization and AR symptoms in a population-based sample of 2320 subjects attending a public fair in the region of Flanders, Belgium. The adjusted prevalence of sensitization was 13.2%, 25.6% and 25.9% for tree pollen, grass pollen, and HDM respectively. Globally, 40.3% was sensitized to one or more of the tested aeroallergens. Men were more allergic than women, especially to HDM. Allergy increased at young age to reach a maximum between 20-40 years and decreased later in life. In sensitized subjects, we evaluated the prevalence of AR using a clinical symptom-based diagnosis. The majority of the sensitized patients (81%) reported allergic symptoms, resulting in a standardized prevalence of 30.9% for AR.

Our study provides new insights into the epidemiology of allergic sensitization and AR. Given the high prevalence of allergy, it is surprising that there is only a limited amount of data on prevalence of sensitization versus AR symptoms. Most studies assessed AR prevalence by questionnaire (4-6), using varying diagnostic criteria to define presence of AR, most of which have not been validated against a gold standard diagnosis (11). Some studies subsequently included a clinical phase in positive subjects only (2), in which SPT was done. In contrast, we evaluated SPT in the general population and identified AR patients using a clinical symptom-based diagnosis. Our assessment of AR closely resembles a gold standard diagnosis of history taking, clinical examination and allergy testing; this study is unique in applying a clinical diagnosis to the general population.

It is difficult to compare our data with earlier results. Most recent studies had some sampling limitation in terms of age, geographical coverage or comorbidity. Bauchau and Durham (2) assessed the prevalence of AR among European adults by means of telephone interviews and

subsequent clinical and IgE-specific confirmation of the positively screened subjects. They found an overall European prevalence of 22.7%, while the Belgian rate was 28.5%. This is highly consistent with the prevalence found in the current study, which is 30.9%. A higher difference could be expected because we also included children, but Bauchau et al. tested for more allergens. The Belgian region of Antwerp participated in the ECRHS (5) and ISAAC (6) studies, and a prevalence of AR was found to be 20.9 to 25.1% in the 20-44 year age group, 5.8% in the 6-7 year olds and 16.9% in 13-14 year olds. In a survey, conducted by Bachert et al. (4), an AR prevalence of 29.8% was found in a representative Belgian population.

The overall prevalence of positive SPT was 40.3%. Sensitization to the individual allergens was 25.9% to HDM, 25.6% to grass pollen, and 13.2% to tree mix. An ECRHS study (12) reported a prevalence of 25.5% sensitized to HDM, 12.2% to timothy grass, 6.9% to birch, and 34.1% overall in 20-44 year aged subjects. Our data of this age group were higher than the percentages mentioned above, and might reflect differences in sampling methodology and the used allergen panel.

According to previous literature, 90.5% of all Belgian sensitized subjects could be revealed by testing with the three most prevalent allergens (house dust mite, grass mix, birch) (13). Assuming that our sample was comparable to that of the aforementioned study, extending the number of allergens tested to 9 would theoretically increase our estimates of overall sensitization by 10%.

We found an increase in allergy at young age to reach a maximum in the third and fourth decade and a decrease in later life. A large review of the available literature about the epidemiology of AR showed that its prevalence has increased over the last decades, in particular in countries with low prevalence (14). The interaction between genetic and

environmental factors seems to be crucial. However, lifestyle changes such as westernization, urbanization and affluence recently received more attention (15). Consequently, it is to be expected that the worldwide prevalence of atopy and AR will further grow. On the other hand, the increase in the number of AR patients seems to recede in countries with high prevalence (14). In western countries, we still might expect an increase in the general AR prevalence, because the present 20-40 year old generation will grow older in the next decades, while a substantial proportion, but probably not longer or only restrictedly growing, of young children will have AR.

We observed a higher prevalence of HDM sensitization in men. These results are consistent with the observation that positive SPTs, especially for HDM, are more prevalent in young boys than girls (16). A change to female predominance is seen in adolescence (17,18), which is also seen in our study. In contrast with previous reports (19), we found a significantly higher prevalence of overall SPT positivity in men. This gender difference in our study was largely attributed by differences in HDM sensitization. Indeed, HDM sensitization has been reported to be predominantly present in male persons, both children and adults (20).

Because the clinical relevance of a positive SPT often is uncertain, we also assessed the presence of allergy symptoms in relation to allergen exposure. Four out of five sensitized subjects experienced symptoms of AR. This number is consistent with results of Burbach et al. (7), who studied clinical relevance of SPTs based on Global Asthma and Allergy European Network (GA(2)LEN) data. Interestingly, skin prick test-positive subjects without symptoms are at risk to develop allergic symptoms (21). However, by thorough exploration of the clinical history, Assing et al. (22) showed that of these asymptomatic subjects developing symptoms, the majority had already had symptoms before inclusion or even denied

symptoms. When history and SPT do not match, a thorough history exploration combined with a symptom diary could demonstrate additional AR patients.

We analyzed risk factors for having AR symptoms in those who were sensitized. The number of sensitizations strongly predicted symptom presence, which is in line with previous observations (7). When having a positive SPT for grass pollen or HDM, women were significantly more prone to experience symptoms than men. This is in sharp contrast with the prevalence of sensitization, which was more common in men. This disparity was also observed in a meta-analysis, showing HDM sensitization to be more prevalent in men, but allergic airway symptoms tending to show a female predominance (20).

Another predicting factor of symptom presence is the wheal size of the SPT. When the wheal size of HDM and grass pollen allergens increased, there was a significantly higher risk of experiencing AR symptoms. A quantification of atopy by means of reporting IgE levels and skin test diameters has already been proposed because of the positive correlation of higher values with the probability of rhinitis (23). However, we have to take into account the contribution of psychological factors to patient perception of allergy symptoms. In some studies, no correlation between symptom severity and age or sex, nor wheal size could be found, but some behavior traits could partly explain symptom reporting (24).

We analyzed the prevalence of sensitization to different allergen groups (grass pollen, tree mix and HDM), and compared this to the expected prevalences (based on prevalence of sensitization to the single allergen groups). All possible combinations of allergen groups occurred more frequently than chance alone would suggest, indicating that sensitizations do not occur independently. These results indicate evidence for the concept of atopy as a

constitution. Previous studies showed that polysensitization is very common in the European general population (25). Moreover, a large group of monosensitized children developed additional sensitizations at older age (26). Possible explanations are a defect in the epithelial barrier, and the IL-4 promotion of T_H2 differentiation, which might be responsible for the observation that sensitization to one allergen can enhance systemic and airway T_H2 responses to a second allergen (27). A recent study concluded that children remaining monosensitized, showed a significantly higher production of IL-10 and IFN- γ , both involved in the T-regulatory cell/T_H1 cascade (28). Furthermore we observed that in sensitizations to two allergen groups, the risk ratio of grass pollen and tree mix was higher than combinations with HDM, which is in line with findings that HDM showed the highest rate of monosensitization (29).

We must interpret the results of this study with care. A selection bias is possible, due to the spontaneous entry of visitors. Allergy sufferers showing a higher interest in participation could cause overestimation, although those with a known diagnosis could show decreased interest as well. Moreover, the population visiting an annual fair could be biased by age, sex and socio-economic factors. Women and 60 to 69-year-olds were slightly overrepresented, which we eliminated by standardization. Lastly, our study was carried out in September, possibly impacting the prevalence of symptomatic grass allergy differently than other allergens due to recall bias.

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266 The opinions, results, and conclusions reported in this paper are those of the authors and are
267 independent of the funding sources. The corresponding author had full access to all data in the study
268 and had final responsibility for the decision to submit for publication.

Conclusion

In this population-based cross-sectional study, we demonstrated a 40.3% prevalence of a positive SPT to one or more common aeroallergens. A clinical diagnosis of allergic rhinitis was present in 30.9%. This study does not only show sensitization and rhinitis symptoms, but links those for each individual allergen, demonstrating that 80% of subjects have symptoms related to the individual SPT results, with no large difference between allergens. Both a positive SPT and AR peak in the third and fourth decade of life. It is to be expected that in the next decades, when this generation will grow older, the general AR prevalence will further increase.

Abbreviations

AR: allergic rhinitis

HDM: house dust mite

SPT: skin prick test

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364

365 **Figures**

366 Figure 1: Age and gender differences of sensitization and allergic rhinitis.

367 Graphical representation of age and gender differences in positive skin prick tests (lines, black
368 box line = female, white box line = male) and symptomatic sensitization (AR; bars, black bar
369 graph = female, white bar graph = male). (A) Tree pollen; (B) House dust mite; (C) Grass
370 pollen; (D) At least one allergen.

371

372 **Tables**

373 Table 1: Unstandardized and age and sex standardized prevalence rates of sensitization
 374 (defined by positive skin prick test) and allergic rhinitis (defined by positive skin prick test
 375 with symptoms).

Outcome	cases	n	Crude prevalence	Standardized prevalence	95% CI	
sensitization						
tree mix	316	2317	13,6%	13,2%	11,7%	15,0%
grass mix	555	2320	23,9%	25,6%	23,3%	28,0%
HDM	564	2318	24,3%	25,9%	23,6%	28,3%
any sensitization	887	2317	38,3%	40,3%	37,5%	43,3%
sensitization + symptoms of AR						
tree mix	223	2263	9,8%	9,7%	8,3%	11,2%
grass mix	370	2245	16,5%	17,6%	15,7%	19,7%
HDM	367	2240	16,4%	17,1%	15,2%	19,1%
any allergic rhinitis	656	2236	29,3%	30,9%	28,4%	33,6%